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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/673,871	10/20/2000	Alexandre Marti	NITROS P146US	6986

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KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER	
CHONG, YONG SOO	
ART UNIT	**PAPER NUMBER**
1617	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/673,871	MARTI ET AL.	
	Examiner	Art Unit	
	Yong S. Chong	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19,20,22-27 and 29-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19,20,22-27,29-35 and 54-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/21/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

This Office Action is in response to applicant's arguments filed on 1/3/2007. Claim(s) 1-18, 21, 28 have been cancelled. Claim(s) 54-67 have been added. Claim(s) 19-20, 22-27, 29-67 are pending. Claim(s) 20, 24-25, 31-35 have been amended. Claim(s) 36-53 have been withdrawn. Claim(s) 19-20, 22-27, 29-35, 54-67 are examined herein.

Applicant's amendments have rendered the 112 rejection of the last Office Action moot, therefore hereby withdrawn. Applicant's arguments have been fully considered but found not persuasive. The 103 rejection of the last Office Action is maintained for reasons of record and modified below for Applicant's convenience.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 19-20, 22-27, 29-35, 54-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gierskcky et al US Patent 6,034,267.

Gierskcky et al teaches pharmaceutical compositions for treating or diagnosing a condition comprising an ester of Aminolevulanic acid (AlA). (see abstract, claim 1) and a pharmaceutical carrier or excipient (claim 8). The concentration of the compounds in Gierskcky's compositions depends upon the nature of the compound, the composition, mode of administration, and the patient and may be varied or adjusted according to choice. Generally, however, concentration ranges of 1 to 50% are suitable (see col 6, lines 25-33). Gierskcky also teaches the use of chelating agent such as EDTA, deferroxamine, or alike in his compositions (see col 7, lines 21-33). Gierskcky teaches methods of preparing and using ALA hexyl ester (see example 4, and 15).

Gierskcky fails to specifically use concentrations of ALA-esters in amounts less than 1% and further specify the instant ranges of pH.

However, it is well established that merely selecting proportions and ranges is not patentable absent a showing of criticality. *In re Becket*, 33 USPQ. 33 (C.C.P.A. 1937). *In re Russell*, 439 F.2nd 1228, 169 U.S.P.Q. 426 (C.C.P.A. 1971). Accordingly, absence of showing a criticality, it would have been *prima facie* obvious to optimize the concentration of Grierskcky's ALA-esters and their respective pH ranges, because it has been held that the ordinary artisan would have had a reasonable expectation of success in achieving the desirable clinical outcome by modifying the such values.

Response to Arguments

Applicant argues that none of the references teach or suggest that toxicity associated with the use of higher concentrations of ALA esters can reduced at concentrations below 1%.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant first argues that there is no suggestion to one of ordinary skill in the art to prepare an ester of 5-aminolevulinic acid at a concentration of less than 1% by weight.

In response, Examiner states that contrary to Applicant's reasoning modification of proportions and ranges is not patentable, as a matter of law, unless there is a showing of criticality. See *In re Becket*, 33 USPQ, 33 (CCPA 1937). *In re Russell*, 439 F.2nd 1228, 169 U.S.P.Q. 426 (CCPA 1971). Applicant has not met the burden of showing that the instantly claimed ranges are critical to operation of preparing a solution that contains an ester of 5-ALA. Furthermore, mere optimization of ranges will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "When the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimal or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 456,

105 USPQ 233, 235 (CCPA 1955); see also *In re Peterson*, 315 F. 3d at 1330, 65 USPQ 2d at 1382 "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages." MPEP 2114.04.

Nonetheless, Gierskcky et al. has provided a suggestion and motivation for modifying or adjusting the concentration ranges of the employed compounds. The concentration of the compounds in Gierskcky's compositions depends upon the nature of the compound, the composition, mode of administration, and the patient and may be varied or adjusted according to choice. Generally, however, concentration ranges of 1 to 50% are suitable (see col 6, lines 25-33). Therefore, the range of 1 to 50% is merely a preferred range and is by no means bound to that particular range.

In response, Gierskcky et al. teaches pharmaceutical compositions for treating or diagnosing a condition comprising an ester of ALA. (see col 3, lines 1-30). Gierskcky teaches the concentrations of the compounds in Gierskcky's compositions are generally about 1 to 50% (see except the instantly claimed ranges of ALA esters. (col 6, lines 24-33). Gierskckcy also teaches the use of chelating agent such as deferroxamine or alike in his compositions (see col 7, lines 21-33). Gierskcky teaches methods of preparing and using ALA hexyl ester (see example 4, and 15). All elements of the instant claims are described in Gierskcky, except the instantly claimed ranges ester of ALA. But as the matter of law, absence of showing a criticality, it would have been *prima facie* obvious to optimize the concentration of Grierskcky's ALA-esters and their respective pH ranges to achieve a desirable clinical outcome. Therefore, the difference is not about two orders

of magnitude higher than presently claimed. Gierskcky et al. would have had a reasonable expectation of success for preparing a composition comprising ALA esters of less than 1% by weight for use in either photochemotherapy or diagnosis.

Further, the Declaration under 37 CFR 1.132 filed January 16, 2004 is insufficient to overcome the rejection of claim 19-27, 29-35 based upon Gierskcky as set forth in the last Office action because: it is not commensurate with the scope of the claims and does not provide adequate data comparing the formulations of Grierskcky to establish unexpected of lower ranges ALA esters of the claimed invention.

As the initial matter the opinion declaration explains methods of using esters of ALA at a lower concentrations as conventionally employed in the art at the time of publication of the cited references. Such studies did not describe unexpected observations in formulating lower concentrations of esterified ALA. Therefore, Applicant's arguments that preparing a formulation of esterified 5-ALA are not commensurate with the scope of the claims, because the instant claims are not directed to methods of using such compositions.

Finally, Applicant argues that it was unexpected that lower doses of ALA esters would produce higher levels of PpIX than the known lowest doses of ALA esters studied at the time of the present invention. Specifically, attention is drawn to Exhibit E, where a graph of ALA esters (concentration) vs PpIX fluorescence is shown.

After closer examination of the graph, Examiner argues that these results are not unexpected because the maximum fluorescence of ALA-ethylester and ALA are above 1% in concentration. The ALA-octylester is inconclusive because there were

precipitation problems at concentrations higher than 0.1%. The ALA-butylester still shows significant fluorescence well above 1%. In fact, ALA-hexylester is the only one that shows the entire fluorescence range well below 1%. With results like this, it is obvious to optimize the concentration below 1%, especially because of the fluorescence results for several ALA esters at or around 1% concentration.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong S. Chong whose telephone number is (571)-272-8513. The examiner can normally be reached on M-F, 9-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SREENI PADMANABHAN can be reached on (571)-272-0629. The fax

phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

YSC

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